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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/122,588	07/23/1998	SEAN C. SEMPLE	016303-00531	4561

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EXAMINER

SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application N .

09/122,588

Applicant(s)

SEMPLE ET AL.

Examiner

Mary M. Schmidt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 September 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 62-83 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 62-83 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 July 1998 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Sept. 26, 2002, has been entered.

### ***Oath/Declaration***

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Changes to the address have been made for the following inventors:

Yuan-Peng Zhang, Mark Reynolds, and John Min.

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***Drawings***

3. The drawings are objected to because of the informalities listed in the attached PTO-948.

A proposed drawing correction or corrected drawings are required in reply to the Office action.

The objection to the drawings will not be held in abeyance.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 62-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating neoplastic cells in cell culture and solid tumors *in vivo* via administering a PEG-ceramide conjugate/lipid/nucleic acid catalyst composition and methods of administering VEGF ribozyme of SEQ ID NO:1 encapsulated in DOTAP/EPC/PEG-Ceramide-C8 (Example 2, page 30 of the specification), EPC:CHOL:DODAC:PEG-ceramide-C20 (50:25:15:10) (Example 4), EPC:CHOL:DODAC:PEG-ceramide-C20 or -C8 (50:25:15:10) (Example 6) for inhibiting solid tumors, does not reasonably provide enablement for methods of treatment of any neoplasm via administration of any PEG-ceramide conjugate, lipid, nucleic acid catalyst composition as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

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Applicant's arguments filed 09/26/02 have been fully considered but they are not persuasive.

Examples 4 and 5 teach the following formulations synthesized via method (1) having the claimed limitations of a PEG-ceramide conjugate, a lipid and a nucleic acid catalyst (a ribozyme): EPC:CHOL:DODAC:PEG-ceramide-C20 (50:25:15:10) with VEGF ribozyme, EPC:CHOL:DODAC:PEG-ceramide-C8 (50:25:15:10) and VEGF ribozyme for injection into mice. The specification teaches on page 35, lines 14-16 the administration of EPC:Cholesterol:PEG-Cer-C20:DODAC (50:25:15:10) formulated VEGF-R-1 (example 6 and figure 9). The specification teaches delivery of liposomes made by method (2) (EPC-DOTAP:PEG) and VEGF ribozyme in saline (non-formulated) via intravitreal injection to mice. The specification further teaches EYPC(egg yolk PC):DOTAP-PEG C8 liposome delivery.

Example 6 in the specification as filed teaches delivery of Lewis lung carcinoma cells to C57/BL6 female mice and jugular vein administration of EPC:Cholesterol:PEG-Cer-C20:DODAC (50:25:15:10) formulated VEGF-R-1 ribozyme and inhibition of the tumor growth.

Applicant's response filed September 26, 2002, cites the work of Pavco et al., *Clinical Cancer Research* Vol. 6, pp. 2094-2103, May 2000, as teaching the efficacy of anti-VEGF ribozymes in treatment of human colorectal carcinoma in male nude mice. They taught on page 2097, col. 1, that tumors were innoculated in the spleen and that the ribozymes were administered via osmotic pump. They also taught use of the anti-VEGF ribozymes in C57BL/6 mice innoculated with Lewis lung carcinoma like the experiments in Example 6 of the instant

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specification. This reference teaches on page 2098, col. 2, that "[N]eovascularization of Lewis lung carcinoma tumors depends on VEGF...." The reference also teaches the ubiquitous nature of VEGF expression in solid tumors and its role in the development of angiogenesis.

Thus a correlation is known in the art that inhibition of VEGF in solid tumors has an effect of decreasing the blood flow to growing tumors. The scope of enablement rejection has been modified accordingly to reflect both the enablement in the art to inhibit VEGF in solid tumors *in vivo*, and also with the expectation that some such solid tumors may be inhibited in human as well. The rejection is maintained on the grounds that the demonstrated Lewis lung carcinoma data and colon cancer data in the Pavco et al. paper with anti-VEGF (anti-Flt) and anti-KDR ribozymes does not correlate to an expectation of success for administration of any ribozyme to any gene target in the claimed liposome compositions for the treatment of any neoplasm as broadly claimed for the following reasons:

The claims are drawn to methods of treating a neoplasia in a mammal comprising administering to the mammal a pharmaceutical composition comprising a polyethylene glycol (PEG)-ceramide conjugate, a lipid, and a nucleic acid catalyst, whereby a therapeutic result is attained. In order for a therapeutic result to be obtained for treatment of a neoplasm in a mammal, the nucleic acid catalyst (exemplified in the specification as a ribozyme) must function in a therapeutic capacity. Thus design and use of the nucleic acid catalyst in a cell *in vivo* is an essential component of the claimed pharmaceutical compositions used in the claimed methods. Thus the instant rejection addresses both aspects of the claimed methods, the use *in vivo* of the

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nucleic acid catalyst, and the use *in vivo* of the PEG-ceramide conjugated/lipid encapsulation of the catalytic nucleic acid for the claimed functions of achieving a therapeutic result in the treatment of neoplasms in the mammal.

In the instant case the claims are drawn to delivery of a catalytic nucleic acid (ribozyme)-liposome complex into a mammal for any therapeutic effect in treating a neoplasm. Konopka et al. teach that "the delivery of functional ribozyme into cells by cationic liposomes is an inefficient process and needs extensive improvement before it can be used in *ex vivo* and *in vivo* applications (see abstract)." The specification as filed does not provide any guidance as to whole organism application other than injection of the specifically formulated VEGF-R-1 ribozyme into mice. Putnam et al. further taught on page 157 that "[a] drawback of liposomes is their relatively short circulation time. Liposomes are rapidly recognized by the reticuloendothelial system (RES)-- typically by monocytes and macrophages in the liver and spleen-- and taken up by endocytosis and deactivated. If the targeted site is within these RES cells, then liposomes are excellent delivery systems; however, the targets are often elsewhere in the body. Advances in liposome technology have created liposomes whose circulation times have been increased by minimizing their recognition by the RES. For example, polyethylene glycol added to the surfaces of liposomes repels proteins involved in their recognition and therefore increases their circulation time. Polyethylene glycol-modified liposomes are also known as Stealth liposomes...." Thus for applications of the claimed liposomes for delivery of any nucleic acid catalyst, such as any ribozyme, to whole organisms for any therapeutic effect must consider factors such as: (1) drug

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leakage from the liposome, (2) hydrolysis of the liposome, (3) uptake of the liposome by the RES system or other undesired immune responses, (4) targeting the liposome to the desired tissue(s) or cell(s), and (5) delivery of the drug into the cell and further success of the delivered drug.

Fritz et al. and Chirila et al. teach common concerns in the design of suitable delivery vehicles for antisense oligonucleotides, which are analogous to ribozymes in many respects: they are both short, oligonucleotides that must target the gene or mRNA of the gene in the cell for degradation. Fritz et al. teach on page 272 that “[a]n efficient and versatile drug carrier system has to fulfill the following requirements: (I) particle sizes in the submicrometer range; (ii) the possibility of surface modification; (iii) high drug loading capacity; (iv) colloidal stability of the latex in biological media; and (v) the lack of toxic side effects induced by the carrier or additives.” Chirila et al. teach on mechanism of antisense action *in vivo* and the necessary requirement that the antisense be able to internalize into the desired cell target (see page 325). They teach on page 327 that “[e]ncapsulation or incorporation in liposomes is currently the preferred method for the delivery of AS ODNs... and, besides the intravenous infusion and subcutaneous, intramuscular or intraocular injection of naked ODNs, probably the only other method used in human clinical trials. (Ultimately, the suspensions of liposomes are also administered by infusion or injection.)” They also teach that the “*in vivo* delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNs in tissues.” Without further guidance in the specification as filed for mechanisms for administration of any ribozyme to particular



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locations in the mammal, one skilled in the art would necessary practice "trial and error" experimentation to design and implement successful regimens for administration of any ribozyme for the claimed therapeutic functions.

In regards to the specific type of nucleic acid catalyst (ribozyme) used, there is a high level of unpredictability known in the art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding. The following references which teach the unpredictability in the art for design and use of antisense to mammals are considered to provide an analogous teaching for ribozymes since ribozymes and antisense have closely related issues for administration *in vivo*. Note Branch, and note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other

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effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunately, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

*In vitro*, antisense/ribozyme specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense

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molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo*: it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

In conclusion, there are numerous obstacles in the art for design of therapeutic nucleic acid catalysts such as ribozymes for use in cells in a whole organism mammal. The nature of the instant invention for treatment of any type of neoplasm in any mammal requires a significant amount of "trial and error" experimentation to overcome the unpredictable factors argued above for the breath of liposomally encapsulated ribozymes instantly claimed. One of skill in the art

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would not accept on its face the successful delivery, and further treatment effects of the claimed catalyst compositions in whole organisms other than mice, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor the technology today teach general guidelines for successful delivery or treatment effects of such liposome - ribozyme compositions in whole organisms. There is no teaching of a correlation between administration of the disclosed VEGF ribozyme for treatment of solid tumors and the administration of ribozymes to any other gene target for treatment of any cancer via any putatively therapeutic ribozyme as broadly claimed. Specifically the specification does not teach design and stability of the ribozyme liposome composition *in vivo* for delivery of any ribozyme to any gene target other than VEGF nor entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects via the catalytic molecule. These key factors are those found to be highly unpredictable in the art. Due to the lack of guidance in the specification as filed for the unpredictable factors argued above, one of skill in the art would have necessarily practiced an undue level of experimentation to make and use the breath of the claimed methods in cells in a mammal for treatment of any neoplasm.

### ***Response to Arguments***

Applicants' state on page 2 of the response filed 09/26/02 that "in view of the state of the art, the use of the presently claimed liposomal ribozyme compositions in any whole organism is entirely routine. The Examiner has provided no evidence that undue experimentation would be

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required to practice the invention in organisms other than mice, such as humans. The specification provides substantial teaching regarding how to make the claimed liposomal ribozyme formulations and how to administer the liposomal ribozyme formulations to a mammal, including humans, having neoplasia.... several Examples are provided in the specification that teach the administration of the formulation to mammals and that unequivocally demonstrate the stability, tumor cell targeting, and ability of the formulations to inhibit the growth of tumors *in vivo*. Apparently, the primary basis for the Examiner's assertion of undue experimentation is the fact that the specification does not provide data showing that the liposomal compositions function effectively in whole organisms other than mice."

The unpredictable factors recited above are not simply solved by routine experimentation, but rather require the *de novo* determination of the key steps in the methods claimed, the design of the ribozymes and the discovery of the routes of administration for the claimed therapeutic effects. The non-prophetic, working examples taught in the specification as filed are further addressed above as being enabling for the breadth of ribozymes and liposomal compositions taught in the specification as filed. It was argued that for each of these points, there is no correlation to an expectation of success for the use of other ribozymes, liposomal compositions for use in any mammal as broadly claimed. However, the claims are now considered enabled for administration of the claimed ribozyme to human.

Applicants further provide the declaration of Dr. Sandra K. Klimuk which "attests to the universality of the belief among scientists that work in experimental animals, such as mice, is of

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critical importance and relevance to other animals, including humans.” Point No. 7 of the declaration (page 2) refers to the examples in the specification as filed as “accurate predictors of the ability of the presently claimed liposomal ribozyme compositions to function effectively in human and mammals other than mice. There is a large body of scientific literature describing the use of mouse disease models to elucidate the pathogenesis of various diseases and to identify drug targets. In view of this, it is clear that other scientists agree that the work in experimental mammals is of critical importance and relevance to other mammals, including humans.”

In response, the fact that murine models are important generally in the pharmaceutical drug discovery process is not attested. However, as reiterated above, in regards to the breath of the instant claims, the examples in the specification as filed are not considered predictive of the breath of functions claimed, treatment of any neoplasm in any mammal. In the instant case, specific and not general guidance is what is needed to teach how to make and use any ribozyme liposomal pharmaceutical composition for treatment of any neoplasm. In point no. 8 (page 3) applicant further discusses the Crystal reference. Applicant points to the Pavco et al. reference to teach support of *in vivo* use of VEGF ribozymes. However, while this teaching does support the enabled breath of the VEGF-ribozyme-liposome composition, the teaching of Pavco et al. is not further considered to teach enablement for the breath of treatment effects of any ribozyme on any neoplasm for the same reasons the teachings of the instant specification as filed (also using C57BL/6 mice) are not considered enabled for the breath claimed.

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Applicant further states in the response on page 4 that “in view of the attached declaration and *In re Jolles*, data in mice is more than sufficient to enable the invention in other organisms, including humans.” In regards to *In re Jolles*, 206 USPQ 885 (CCPA 1980), the decision by the Board referred to rejection under 35 U.S.C. 101 utility, which was not analogous to the grounds of rejection instantly made under 35 U.S.C. 112, first paragraph. It is not argued in the instant case that the claims do not have a patentable utility. It is agreed in the instant case that the claims to methods of treatment do have a patentable utility. The instant rejection over the ability to make and use the breath of claimed pharmaceutical compositions for the utility of treatment of any type of neoplasm in any mammal is thus different in emphasis and content that the rejections made in *In re Jolles* arguing a lack of patentable utility.

Applicants further state on page 4 of the response that “Applicants respectfully submit that the Examiner has provided no reason why one of skill in the art would expect the pharmacokinetic behavior of liposomes containing other ribozymes to differ significantly from those containing the anti-VEGF ribozyme. The increased stability and cellular targeting *in vivo* of the liposomal compositions of the present invention are a consequence of the liposome encapsulating the ribozyme, rather than the catalytic properties of the encapsulated ribozyme. Therefore, the liposomal compositions of this invention containing any nucleic acid catalyst should be delivered to neoplastic cells *in vivo* to approximately the same degree as the liposome-encapsulated neoplastic cells *in vivo* to approximately the same degree as the liposome-encapsulated anti-VEGFR ribozyme.” Applicant has not addressed the fact that the claims are

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drawn to the function of treatment of a neoplasm. The use of different ribozymes to different target genes would have an expectation to function vastly differently for the treatment of any type of neoplasm. New references have been cited to teach the unpredictability in the art for the design of ribozymes to any target and the use of liposomes for encapsulating ribozymes for *in vivo*. The complexity of the breath of the claimed methods is very high. Thus there is not an expectation of success that the use of different ribozymes in the same liposomes will have the same therapeutic effects instantly claimed. Each ribozyme must be considered on an individual basis due to the high level of unpredictability in the art cited above, and the unique nature of targeting a different gene and the effects that would have on the mammal.

6. The claims drawn to methods of treating a neoplasia in a mammal via administering to a mammal a pharmaceutical composition comprising a polyethylene glycol (PEG)-ceramide conjugate, a lipid and a nucleic acid catalyst whereby a therapeutic result is attained, are free of the prior art since the prior art did not teach nor fairly suggest an expectation of success for administration of any such ribozyme encapsulated in PEG-ceramide conjugates and a lipid having the claimed therapeutic effect in treatment of neoplasms *in vivo*.



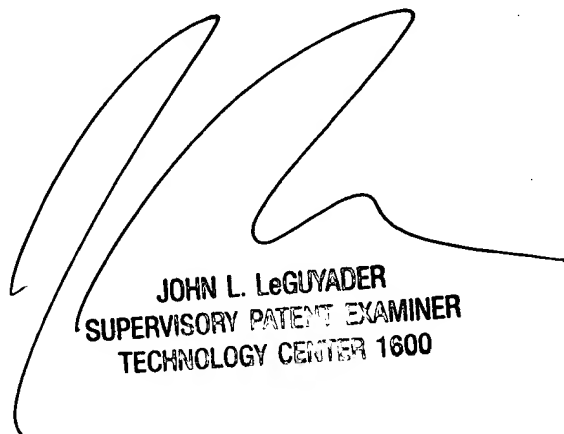
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7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt  
January 28, 2003



JOHN L. LeGUYADER  
SUPERVISORY PATENT EXAMINER  
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